Richard L. Wolgemuth, Ph.D.
Senior Vice President
Global Regulatory Sciences
Pharmaceutical Research Institute

P O Box 4000 Princeton, NJ 08543-4000
Tel 609-252-6503 Fax 609-252-7350
Richard.Wolgemuth@bms.com

Bristol-Myers Squibb Company

April 11, 2005

Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2005D-003D; Draft Guidance, Draft Guidance for Industry on Clinical Lactation Studies - Study Design, Data Analyses, and Recommendation for Labeling, 70 Federal Register 6697 *(February 8, 2005).*

Dear Sir or Madam:

Bristol-Myers Squibb (BMS), a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, infant formulas, and nutritional products, is pleased to have the opportunity to offer comments on the above draft guidance. Our company's mission is to extend and enhance human life by providing the highest-quality pharmaceutical and related health care products. For this reason, we are interested in commenting on the draft guidance. Our comments are set forth below.

Summary of BMS Comments on Proposal

BMS appreciates the importance of optimizing prescribing information for women needing medication while breastfeeding their infants. We know that breastfeeding provides important nutritional and immunologic benefits to an infant that may be affected if breastfeeding is interrupted or discontinued because of maternal need for medication. Alternatively, if breastfeeding is continued while a woman is treated for an acute or chronic medical condition, there is concern for drug transfer to the infant and the potential for adverse drug effects. In addition, little information is available on pharmacokinetic and pharmacodynamic changes (if any) which occur in women who are lactating (or on their milk production), and if these changes are clinically significant.

With only limited information in the published literature and product labels, we agree with FDA that there are circumstances where additional pharmacokinetic and clinical safety information may be useful for prescribers and their nursing mothers. We agree that certain drugs or classes of drug (e.g., anti-depressants, analgesics, and anti-infectives) are likely to be used by breastfeeding women, and data from clinical lactation studies may be very helpful for prescribing these agents or adjusting drug doses. We also agree that conduct of these studies would not usually be considered until after marketing approval when general efficacy and safety for a drug are known, and there is evidence that the drug will be used by breastfeeding women. However, for agents such as vaccines or radioimaging products where lactating women are less likely to be

intentionally exposed and the risks may be significant, we strongly believe that alternate strategies for data collection in mothers and infants can be developed. Agents such as these will have persistent markers and women with inadvertent exposures can be enrolled in a special registry that includes referral for pharmacokinetic/pharmacodynamic sampling as part of a clinical study assessment. In addition to these general comments, we would like to provide comments on specific sections of the Guidance:

III. Considerations for When to Conduct a Clinical Lactation Study

BMS agrees with the Agency that data from clinical lactations studies would be helpful when there is evidence of use or anticipated use of the drug by lactating women. If a drug is not anticipated to be used in lactating women, although indicated in women of childbearing potential, these studies may not be necessary. Study requirements for approved and marketed drugs should be based on evidence that a drug is frequently used by breastfeeding women or reports of adverse events in mother or infant associated with maternal use of the product. Reports of the need for dose adjustment to maintain the drug's clinical efficacy in lactating women may also warrant controlled studies. As FDA noted in the Guidance, information suggesting the need for clinical lactation studies could be based on specific adverse event reports received by the sponsor, published literature and/or medical specialty group consensus or opinion papers.

Lines 166-169 We disagree with FDA's general statement that vaccines and radioimaging agents be considered for human lactation studies. We strongly recommend that these studies, if needed, be restricted to "lactating women only" study designs. For vaccines, mother-infant pair study design can probably follow for most vaccines if there are no concerns from the lactating-only studies. However, for radioimaging agents, mother-infant pair study design should be limited only to situations where there has been inadvertent infant breastfeeding following maternal exposure. In these instances, mother and baby can be enrolled in a registry which would refer them to a clinical lactation study.

Lines 171-174 We request clarification of the Agency's statement that "the applicability and predictability of nonclinical models ... are still under consideration, but these models do not help in deciding whether to conduct a study in lactating women." Is FDA considering the use of nonclinical computer modelling methods to assist in prediction of drug transfer to breast milk as a guide to the design of human lactation studies or is the reference to "nonclinical models ... under consideration" meant to describe the possible need for further (more detailed) animal studies in addition to the lactation data obtained from Segment III reproductive toxicity studies?

Lines 200-202 FDA suggests the possibility of "nest [ing] clinical lactation studies within a larger clinical study on safety or efficacy outcomes or in combination with the postpartum assessment of the effects of pregnancy on the PK and/or PD of a drug." We agree that including clinical lactation studies within a larger safety or efficacy trial may be logistically difficult unless only limited PK/PD sampling is needed, and this design should be limited to post-marketing studies only. Inclusion of a lactation study as part of a postpartum assessment in a pregnancy drug exposure study would be reasonable. However, the maternal-infant pair study design should not be used until results from *plasma and milk* or *milk only* studies are available.

IV. Study Design Considerations

BMS agrees with FDA's proposal to exclude mother-infant pair studies until a study of lactating women evaluating *plasma and milk* or *milk only* are performed. We agree that when drug data is available from the pediatric population, this information coupled with maternal lactation data can supplant the need for further studies in the breastfed child. We also agree that the *plasma and milk* or *milk only* study designs will provide data on the extent of drug transfer into breast milk, effect on milk production and milk composition.

A. Mother-Infant Pair Design

We appreciate that the mother-infant pair design may provide a comprehensive assessment of effects on both mother and their individual infants particularly when there is a need to know the amount of drug absorbed by an infant and its effect. We agree with FDA that when necessary, this study design would enroll mother-infant pairs who are planning to or are currently receiving study medication for a treatment indication. BMS feels strongly that this study design should only be considered after assessing data from lactating women only design studies particularly if there are concerns about infant safety associated with drug exposure. In addition, animal perinatal studies (Segment III studies) should also be reviewed for abnormal neurodevelopmental or immunologic effects before initiating these studies and exposing infants to drug in breast milk.

Lines 213 FDA suggests that the mother-infant pair study design can potentially "show effects of drug on milk production and composition." We suggest that this information can be obtained using the *milk only* study design.

Line 236 FDA suggests the mother-infant pair design be used when there is "potential for accumulation in breast milk." Since normal lactation necessitates frequent nursing or manual milk expression, it is unlikely that a drug will be present in breast milk for more than several hours and thus make drug accumulation unlikely.

Lines 238-239 We assume that the statements concerning "wide distribution to multiple organs" and "long half-life" refer to the potential for wide drug disposition and prolonged duration of exposure in the infant based on findings in the mother or previous study populations.

B. Lactating Women Only Design

1. Lactating Women (Plasma and Milk)

The utility of this study design appears most important when there is concern that the normal physiologic effects of lactation itself or the postpartum period may alter maternal drug PK and necessitate dosing modification (increase or decrease) for maternal safety or efficacy.

We agree with FDA that this study design "be considered before the infant is exposed to drug via breast milk in a more complex study."

2. Lactating Women (Milk Only)

Lines 270-284 This study design includes frequent maternal milk sampling "throughout the dosing interval, a specific time period (e.g., a 24-hour period), or the entire time course of lactating (e.g., months)." FDA states that information from lactation studies with this design may be useful in assessing strategies to minimize exposure of the breastfed child to a drug. This study design "can provide information regarding timing of maternal dose relative to breastfeeding, the duration to discard milk relative to maternal dose, and when to resume

breastfeeding relative to maternal dose or drug exposure. A finding that showed the amount of drug in breast milk to be exceedingly low could preclude the need for further studies ... (and) could examine the effect of drug on milk production and composition."

BMS agrees with these statements and recommends that this study design be used as the first-line approach when clinical lactation studies are needed for infant risk assessment whether a drug is used by the mother for short-term, intermittent or chronic therapy.

The need for further studies in a mother-infant pair study design can then be determined based on the drug concentration and duration of exposure or other factors identified in the *milk only* study.

C. Other Design Considerations

l. Longitudinal Design

This study design is suggested for drugs that are administered chronically or for several treatment cycles. We suggest that data from short-term *milk only* and mother-infant pair studies be completed and assessed prior to longitudinal studies so that any potential risks associated with long-term infant drug exposure during maternal chronic or repeat dosing can be minimized.

3. Study Participants

We agree with FDA that study participants should represent a typical patient population for the drug under study and that maternal and infant variables be taken into consideration. However, addressing all potential variables with a single study may be difficult. We suggest rather that maternal and/or infant variables be guided by the disease under study (and/or postpartum period) and that additional study variables reflect safety or efficacy issues identified in other clinical trials (e.g. race, renal function, etc.). In addition, if post-marketing surveillance identifies a maternal or infant subpopulation with possible additional risk factors for drug exposure, then further studies can be considered.

Lines 337-339 We agree that for drugs that are hepatically metabolized and known to exhibit genetic polymorphism, the metabolic status of the mother and infant should be assessed.

4. Controls

Lines 343-348 We suggest that study subjects with the medical condition of interest, and used as control subjects in a study, be described as patients to avoid confusion with healthy volunteers.

5. Sample Size

Lines 356-359 The lactation guidance recommends sizing a study "sufficient [ly] to detect a clinically significant difference." This statement proposes some troublesome differences and is in contrast to the recommendations proposed in the FDA Preliminary Concept Paper on Drug Interaction Studies - Study Design, Data Analysis, and Implications for Dosing and Labeling which better recognizes the exploratory nature of these studies. Lines 625-632 of the Drug Interaction Concept Paper refrain from "recommending the inclusion of some number of subjects" and Lines 580-586 of that document state that the "results ... should be reported as 90% confidence intervals" and that "tests of significance are not appropriate."

Lines 374-375 The comment about the exploratory nature of "*milk only* studies" should apply more generally.

6. Sample Collection and Analyses

Lines 391-400 In order to determine milk consumption and drug concentration in breast milk, we recommend that breast milk be expressed and bottle-fed to infants participating in a lactation study in addition to recording pre- and post-feeding infant weights. Also, the "post-feeding weight [must] account for any infant voiding [vomiting or regurgitation] ... that occurred during feeding."

Lines 405-406 We request additional information on FDA's suggestion to assay milk samples for milk fat. Is this intended to describe/quantify differences in drug concentrations related to drug lipophilicity at different postpartum timepoints (e.g. fat content of colostrum vs. fat content in breast milk later in the postpartum period)?

Lines 408-414 We suggest that it will be difficult to measure drug concentrations in alternative fluids (e.g., saliva, tears). This type of data is rarely readily available in adults, and may be difficult to extrapolate to infants. Under proper conditions, however, accurate infant urine collection can be achieved to measure drug excretion and these results will probably be more accurate than measurements from alternative body fluids.

V. Data Analysis

A. Parameter Estimation

Lines 514-519 FDA recommends calculating the infant drug dose from the M/P ratio using AUCs and assumes a "standardized milk consumption of 150 mL/day, the mean milk intake of a fully breastfed 2 month-old infant." Does the Agency recommend modifying the daily milk consumption estimate for older infants (e.g., 1 year-old child)?

B. Development of Dosing Recommendations for Lactating Women

Lines 544-552 FDA suggests dose or dosing interval adjustments to maintain comparable drug plasma concentrations in both normal adults and lactating patients. We suggest that these adjustments would only be needed if there is a demonstrable lack of efficacy or concerns for clinical safety. If drug efficacy and safety issues are not identified, dose adjustment based on differences in plasma concentrations should only be needed for a drug with a known narrow therapeutic index.

Lines 556-579 The text presented in this section is very similar to Lines 588-617 of the Drug Interaction Concept Paper. Both discuss criteria for concluding "absence of effect" and Line 558 of the lactation guidance still has the phrase "clinical significance of the interaction." However, the drug interaction guidance better recognizes the exploratory nature of these studies.

C. Development of Recommendations to Minimize Infant Drug Exposure from Breast Milk

Lines 593-597 We agree with the Agency's recommendations for informing prescribers about ways to minimize infant exposure to a drug in maternal breast milk.

VI. Labeling

Lines 602-610 We agree with FDA that data from clinical lactation studies be included in the product label. This would include maternal PK/PD results, information on drug concentration in breast milk, infant exposure (if known) and effect on milk production and composition (if known). This information should be included in the Clinical Pharmacology section of the product label.

A. Clinical Pharmacology

2. Special Populations Subsections

Line 649 We recommend replacement of "terminal half-life of Drug X ..." with "duration of effect of Drug X."

B. Precautions/Nursing Mothers

Lines 667-670 FDA recommends adding pertinent information in this section if lactation studies demonstrate clinically important changes. If no significant findings are identified in lactation studies, shouldn't that information also be conveyed in this section?

C. Dosage and Administration

Since most lactation studies will involve only a small number of subjects and results may not be generalizable to a broader lactating population, we recommend that specific dose adjustment should not be provided in this section except for drugs that have shown efficacy or safety concern. For most other drugs, the prescriber should be referred to the Clinical Pharmacology section to determine if dose adjustment needs to be considered for his/her individual patient.

Line 695 A statement describing the relationship between Drug X's clearance and lactation is not clear. Is FDA advising a description of rate of drug clearance and corresponding drug concentrations in breast milk?

Lines 706-709 We agree with a statement included here cross-referencing the Precautions/Nursing Mothers section of the label (if indicated) on ways to minimize infant exposure to drug in breast milk.

VII. Consideration for Future Research

Lines 712-722 In this concluding section, the guidance seems to substantially underestimate the value of nonclinical (animal) models in predicting drug exposures in human breast milk and the resulting infant exposures. While the guidance states that nonclinical (animal) models have demonstrated only limited success in predicting these drug exposures, this situation more likely reflects the inherent limitations of cross-species extrapolation, which exists irrespective of which species is being used for the extrapolation (animal to human or human to animal). Thus, nonclinical lactation models are not likely to be significantly improved by utilizing information from clinical lactation studies, as the guidance suggests.

Conclusions

We recommend that the maternal *milk only* study design proposed by FDA be used as the first-line approach when clinical lactation studies are needed for infant risk assessment whether a drug is used by the mother for short-term, intermittent or chronic therapy. The mother-infant pair study design should follow the *milk only* design if breast milk drug concentrations are considered significant and raise concern for infant safety. If information from pediatric studies is available, a mother-infant pair study may not be necessary. The need for a longitudinal study with potential long-term infant exposure to drug in breast milk should be determined from the results of short-term *milk only* or mother-infant pair studies. The maternal *plasma and milk* study design appears to be most useful when there is concern that the physiologic effects of lactation may alter maternal drug PK and necessitate dosing modification for maternal safety or efficacy. For labeling purposes, we recommend that dosing adjustment in lactating women be considered only when drug efficacy is changed or safety concerns are identified. Finally, we agree with FDA that information, if available, on ways to minimize infant exposure to a drug in breast milk should be included in the product label.

Bristol-Myers Squibb appreciates the opportunity to comment on this Draft Guidance on Clinical Lactation Studies - Study Design, Data Analysis, and Recommendations for Labeling. We hope that our comments are helpful to the Agency and will be considered as the Guidance is implemented. Please feel free to contact us if we can be of further assistance in this matter.

Sincerely,

Richard L. Wolgemuth

Richard L. Wolgemuth, Ph.D.
Senior Vice President
Global Regulatory Sciences